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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,698	09/08/2000	Samuel C Silverstein	60467/JPW/GJG	3655

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01/16/2004

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EXAMINER

VANDERVEGT, FRANCOIS P

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/658,698	Applicant(s) SILVERSTEIN ET AL.	
	Examiner F. Pierre VanderVegt	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
 a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 33-132 have been canceled previously.

Claims 1-32 are currently pending.

In view of Applicant's amendment filed September 29, 2003 only the following ground of rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-32 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It was previously stated: "Briefly, the claims are most broadly drawn to a method of inducing an immune response in a subject having a disease to an antigen. The method includes a) loading the antigen and adenosine triphosphate into a particle, b) coating the particle with a ligand of antigen presenting cells, c) incubating the coated particles with antigen presenting cells (APCs), and d) administering the APCs to the subject and generating an immune response to the antigen.

In the "First Series of Experiments" at pages 32-34 and Table 1 on page 35 of the specification it is disclosed that dendritic cells primed in this manner were capable of stimulating the proliferation of T cells in a standard *in vitro* thymidine-uptake assay, asserting that the assay represent a "CTL assay" at page 35, lines 1-7. However, CTL activity as a measure of specific cellular immunity is more accurately reflected by a cytotoxicity assay, such as a ⁵¹Cr-release assay or a cytokine profile. It is well established in the art that cellular immunity, mediated by NK cells and killer T cells, is a Type 1 activity and that humoral immunity, mediated by antibodies, is a Type 2 activity (see, *e.g.*, page 188, column 1 of Grufman et al (U on PTO-892)).

It is respectfully submitted that it would require an undue amount of experimentation on the part of one skilled in the art to practice the claimed invention. Grufman et al in the paragraph bridging the columns on page 1088 discloses that IL-12 is required for Type 1 responses to cancer antigens and some bacterial antigens, while not being crucial for some other bacterial infections or viral infections. The la Sala et al 2001 reference (V on PTO-892) discloses that incubating dendritic cells in ATP during maturation, *i.e.*, antigen loading, distorts said maturation and inhibits the production of IL-12 by the matured dendritic cells and impairs their ability to initiate Type 1 immune responses *in vitro* (abstract and column 1 of page 1614 in particular). Accordingly, based upon the state of the art, the artisan would not be able to predict that the dendritic cells generated by the claimed method would be able to stimulate an effective killer T cell response to any antigen *in vivo*, irrespective of whether the T cells are stimulated by the dendritic cells *in vivo* (claims 1-16) or *in vitro* (claims 17-32).

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Additionally, and in particular regard to the method of claims 1-16, the specification does not demonstrate, or reasonably suggest success of, the ability of those same dendritic cells to attract cytotoxic T cells *in vivo*. The Ia Sala *et al* 2002 reference (W on PTO-892) discloses that dendritic cells that are treated with extracellular ATP possess a reduced capacity for attracting Th1 and T-cytotoxic (killer) 1 cells. One skilled in the art would not be able to predict that dendritic cells which were primed *in vitro* in the presence of extracellular ATP would be able to attract Type 1 killer T cells *in vivo* for activation versus the loaded antigen.

In view of the lack of predictability in the art to which the invention pertains and the lack of established clinical protocols for therapies based upon the *in vivo* or *in vitro* activation of T cells using artificially manipulated APCs, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inducing a cytotoxic response to an antigen *in vivo*."

Applicant's arguments filed September 29, 2003 have been fully considered but they are not persuasive.

Applicant argues that the references cited cannot be used to cast doubt on Applicant's claimed invention because the specification comprises a working example at pages 32-35 that shows the operability of the claimed invention. The working example in question adequately demonstrates that dendritic cells primed with RBC ghosts loaded with ATP and ovalbumin were capable of inducing cytotoxic T cells to lyse ovalbumin bearing cells. As stated previously, the thymidine uptake assay of the example demonstrates proliferation of class I T cells in response to the dendritic cells, not their lytic ability. Further, the example does not address the issue raised in the cited references that ATP-primed dendritic cells inhibit IL-12 production, which inhibits the ability of the dendritic cells to initiate Type 1 responses to cancer antigens and some bacterial antigens. Further, the working example does nothing to address the issue of the ability of the ATP-stimulated dendritic cells to attract Type I T cells *in vivo*, as the *in vitro* example shows only the interaction of cells which have been placed into proximity with one another by placing them in the same wells/dish. Accordingly, the ground of rejection is maintained.

Conclusion

2. No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing

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date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
January 11, 2004

RV

Pat J Nolan
PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
1/12/04